British Association of Research Quality Assurance
Formerly QAG (UK)
20-22 Queensberry Place, Kensington, London SW7 2DZ

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Direct Line: (01304) 646282

Vic Cracknell
Pfizer Ltd.
Ramsgate Road,
Sandwich,
Kent
CT13 9NJ

Dear Vic,

Many thanks for providing the BARQA Animal Health Committee with the opportunity to review and comment on the draft Step 4 VICH GCP document. I also appreciate the time you spent discussing the document with me.

In general the document appears comprehensive and clearly worded with well defined responsibilities. It is anticipated that these guidelines will provide an easily understood framework against which clinical trials can be conducted.

The following list provides consolidated comments from the committee. Please note that the suggested changes to sections 7.3.6.4 and 7.3.6.5.5 are the two considered by the committee to be of highest priority.

Page 3, 1.3 Suggest that the wording is amended as follows: "....to determine whether the study being evaluated **is/was** properly conducted and whether the data **are/were** recorded...", as audits may take place during the in-life phase of the study.

Page 3, 1.7 Clinical Study. The use of the word experiment in the UK is generally used only in the context of a controlled in-house study ; ie under A(SP)A. We have had discussions with the Home Office in the past regarding what is and what is not covered by the A(SP)A and an ATC. The use of experiment in the context of GCP could cause problems relative to justification of some GCP studies under an ATC. Suggest that the word **'trial'** is used.

Page 3, 1.8 Adherence to relevant SOPs should also be included in the definition of compliance.

Page 4, 1.15 The proposed definition of Investigational Veterinary Product includes any products being evaluated to investigate any physiological effect. This could be interpreted as including feed additives already regulated under 70/524/EC. We believe that non-veterinary compounds already regulated outside the scope of GCP should not be included in this definition. Clarification about whether or not biologicals and growth promoters are covered under GCP would be appreciated.

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Page 5, 1.22 Suggest that this states 'Raw Data **(Source Data)**' to make it more GCP rather than GLP.

Page 5, 1.23 The authorities that review the data may not be the same bodies as conduct the inspections (for example as is anticipated in Europe) - suggest the following wording: "...the expression 'regulatory authorities' includes the authorities that review submitted data and **those that** conduct inspections."

Page 5, 1.25 An SOP is not a document written to 'achieve uniformity' - suggest that **'facilitate consistency'** would be a more accurate definition.

Page 6 , 1.29 The definition does not state that deviations should be documented and whether such documentation should include a statement addressing the effect of the deviation on the trial. It would be useful if guidance were given on signing/dating responsibilities for Protocol Deviations, as per amendments in section 1.28.

Page 7, 2.5 It is unclear as to how the relevant regulatory authority would assure that the requirement for obtaining informed consent from the owner of the animals is established and followed? This sounds like Ethics Review Committee which is not currently established for veterinary protocols. Or is the intention to do this through review of protocols submitted to agencies (not done in Europe) or submitted to obtain permission conduct the trial? Suggest that at a minimum "**..and followed**" is deleted as it would be burdensome on regulatory authorities to assure informed consent for all studies.

Page 7, 2.7 Is it intended to have "good manufacturing practice (GMP)" in upper or lower case? If lower case, also put 'gmp'. Suggest the following amendment "...should be documented and the products **should be** used in accordance with the study protocol."

Page 7, 2.8 The fact that it is 'perceived' that the Sponsor would be responsible for QA functions does not really assign the responsibility - but the flexibility for CRO QA or subcontracted QA needs to be built in. Need to highlight the need for independent QA. The last sentence should use QC instead of QA. Suggest the last two sentences of this paragraph is re-worded as follows: **"The sponsor would be responsible for providing sufficient resource to ensure that QA functions are provided for these studies. The provision of QA functions may be contracted to other parties.** All participants in clinical studies are encouraged to adopt and adhere to generally recognized sound **QC** practices."

Page 8, 3.1.4 "The investigator is employed by the sponsor or a contract research organisation". It would be preferable to state that "the Investigator **will be renumerated** by the sponsor or contract research organization **for work carried out in the course of the study ...**" to maintain the idea of Investigator independence.

Page 8, 3.1.4 "The investigator may be assisted by trained **technical assistants** in collecting....", it would be preferable to say "assisted by trained **competent staff**" as this would also cover the farm situation.

Page 11, 3.2.33 Suggest changing to: "Permit monitoring and quality **control/assurance** auditing of a clinical study. Otherwise this could be interpreted that companies must prove that their auditing is of a quality standard to comply with this sentence.

Page 11, 4.2.3 "...determine their (investigator's) availability for the entire duration..." It may also be worth including a sentence about replacing an Investigator if the original one becomes no longer available (e.g. illness, death etc).

Page 12, 4.2.8.4 Suggest "Communication between investigators is facilitated, **where required**", as it may not always be appropriate for investigators to talk to each other for example if it may affect blinding.

Page 12, 4.2.11 For food animals would it not be sufficient for the Investigator to just ensure **'safe'** disposal of animals/edible products? Otherwise the Sponsor is responsible for carcasses processed through rendering plants or butchers or the sale of milk or eggs to supermarkets. This would be impractical in reality, especially for breeds or in countries where animal passports or other means of tracking individual animals do not apply. Also, how would this apply to companion animals? Also it is unclear whether the intention is for the Sponsor to document that they have followed the eac animal all the way through, or whether the intention is that systems are in place for them to do so if there is an issue or concern.

Suggest rewording: "At the end of the study or withholding period, ensure the safe disposal of all study animals and any edible derived from them."

If this sentence remains unchanged we may find a greater tendency for animals to be slaughtered at the end of trials.

Page 13, 4.2.16 suggest that 'quality **control/assurance** auditing' is used instead of 'quality auditing' - otherwise companies will need to prove that the auditing conducted is of quality - see above.

Page 13, 5.1 "The monitor should be trained in quality control techniques and data **verification** procedures". Auditing is the responsibility of QA.

Page 14, 5.2.7 It is impractical for the monitor to never be any part of record-keeping or data collection. Suggest that this is deleted. Also the monitor should ensure that SOPs are being followed.

Page 16, 6.3.8.1 Suggest changing effectiveness to efficacy: "a placebo control clinical field **efficacy** study".

Page 16, 6.3.8.2 What does 'with specificity' mean? Does this mean 'in detail' or 'specifically'? Does not make grammatical sense.

Page 17, 6.3.11.4 Suggest this is reworded to "describe permissible **and non-permissible** concomitant veterinary care and therapy" to allow for contra-indicated medication for example.

Page 20, 6.3.20.1 Suggest rewording this to "List any **appropriate technical** SOPs that apply to the conduct of the study." It would be cumbersome and of little value to list all SOPs for things like monitoring and reporting as they would be the same for every study conducted by a sponsor. Also these type of SOPs are of no value to the Investigator.

Page 22, 7.3.6.4 This requires a complete description of animal disposal in the report. This could make the final report very large if it has to include data about each animal - a summary only (for example, all animals treated with the test material were euthanised and incinerated following the end of the study or all animals were returned to their owners at the end of the study) with full details available as part of the Trial Master File, should be sufficient. Suggested rewording: "A **summary** of the disposal of the study animals and**/or** their edible products."

Page 23, 7.3.6.5.5 As above, this requires a complete inventory of use and disposal of investigational veterinary products & control products as part of the report, which would make the report large - a summary only (for example, 247 ml of teat article was used in this study, the remaining 153 ml supplied to the Investigator were returned to the Sponsor and incinerated) with full details available as part of the Trial Master File, should be sufficient. Suggested rewording: "**A summary** of the use and disposal of..."

Page 23, 7.3.9.1 More description is required for what is meant by "handling of records" otherwise this will be difficult for people to interpret. Does this mean handling of data records i.e. a description of data management procedures or does this refer to archiving of records?

Page 24, 7.3.9.6 Need clarification about who should sign this statement - suggest the Monitor should sign it.

Page 24, 7.3.10.3 Suggest use the term QA statement as this is recognised industry terminology.

Page 24, 8.1.2 quality **control/assurance** audit - see above

The committee would appreciate if these comments could be forwarded to the appropriate parties for consideration. Many thanks for the time spent in considering our comments.

Yours sincerely

Helen Harlow
VICH GCP representative of the BARQA Animal Health Committee

c.c. BARQA Animal Health Committee